Journal of Saudi Chemical Society (2022) **26**, 101447

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Multistep synthesis and screening of heterocyclic tetrads containing furan, pyrazoline, thiazole and triazole (or oxadiazole) as antimicrobial and anticancer agents

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Received 18 January 2022; revised 14 February 2022; accepted 26 February 2022
Available online 3 March 2022

KEYWORDS

Heterocyclic tetrads;
Cancer;

Abstract In the present study novel heterocyclic tetrads containing furan, pyrazoline, thiazole and triazole (or oxadiazole) (**1**, **2, 3, 4a-e** and **5a-e**) were designed and synthesized and investigated for their antimicrobial (against selected bacteria and fungi) and anticancer potential. The molecules **4e**

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jscs.2022.101447

Microbial infections;
Docking

and **5e** containing 4-fluoro phenyl and 4-fluoro benzyl substituents showed promising antimicrobial (antibacterial and antifungal activities with MICs ranging between 0.5 and 8 μg/mL. Compounds **3** exhibited potent anticancer activity with an IC_{50} value of 0.49 ± 1.45 μM against the human gastric cancer cell line (BGC-823) whereas compound **4e** displayed an IC_{50} value of 0.65 ± 0.53 μM against breast cancer (MCF-7) cell line respectively. All compounds showed selective toxicity against the cancer cell lines compared to human normal liver cell lines. Molecular docking studies of the most potent compounds (**3** and **4e**) against selected microbial and cancer proteins revealed the crucial binding interactions of the potent compounds with the target enzymes. Compounds **3** and **4e** are promising lead molecules to be developed as potential drug candidates.

1. Introduction

Heterocyclic ring structures are distributed in various species as important structural fragments of different primary and secondary metabolites including amino acids, neurotransmitters, vitamins, alkaloids, pigments, antibiotics, flavonoids etc [1]. Heterocycles comprise the core elements in a large number of molecules showing different kinds of pharmacological and biological actions [2–4]. These scaffolds play a central role in different biochemical reactions, biological processes as well as the drug discovery and development [5–7]. They are also the most important pharmacophores for most of the drugs [8]. More than 85% of the bioactive compounds contain one or more heterocyclic rings [9]. The unique properties of the heterocyclic motifs make them attractive to medicinal chemists in their drug discovery programs. Depending on the pH of their environment, heterocycles behave either as acids or bases [10]. Incorporation of heterocyclic scaffolds into the drug molecule will aid in the alteration of physicochemical, pharmacokinetic and pharmacodynamic activities and toxicity profiles of drug molecules [11,12]. Heterocyclic rings present in the lead compounds or the drug molecules can bind with receptors through multiple intermolecular forces like hydrogen bonding, π-π stacking interactions, van der Waals and hydrophobic interactions, dipole-induced dipole as well as the coordinate covalent bond with the metals at the target site [13]. Additionally, the availability of heterocycles of different ring sizes and structural diversities allow them to bind structurally diverse binding sites of the targets. Further, the recent report on the analysis of the structural components of synthetic compounds bearing heterocyclic moieties by Marson et al., had demonstrated that the inclusion of these rings had a crucial role in enhancing the aqueous solubility and target binding as well as decreasing the conformational entropy and formation of toxic metabolites [14].

In view of the above features, heterocycles are playing a central role in the design of novel therapeutic agents including antimicrobial and anticancer agents [15]. Out of the 12 drugs approved by US-FDA in 2021, nine drugs contain heterocyclic scaffold as their essential pharmacophores [16]. Among others, the five-membered heterocyclic rings bearing nitrogen sulfur and oxygen are one of the most attractive scaffolds for organic and medicinal chemists due to their synthetic feasibility and broad-array of pharmacological activities and these rings comprise roughly about top 20 common aromatic rings present in the reported bioactive compounds [17–19]. Typically, medicinal chemists design lead molecules containing more than one heterocyclic ring as this will help the drug molecules to have much drug-likeness compared to the one with mono-heterocyclic rings. Nature-derived and synthetic drugs useful against microbial infections and cancers possess more than one heterocyclic ring [20,21] (Fig. 1).

In view of the above facts and our special interest on the design and synthesis of novel five-membered heterocyclics based antimicrobial and anticancer agents [22–28] herein we report the synthesis, biological and computational screening of novel compounds containing different five-membered heterocyclic systems including furan, pyrazoline, oxadiazole, thiazole and triazole motifs. These heterocyclic rings are privileged scaffolds as they are distributed in drugs used to treat different disorders including cancers and microbial infections (Fig. 2).

2. Materials and methods

2.1. General

The starting material, reagents and solvents used for the synthesis were procured from Fischer Scientific (Mumbai, India), Merck Pvt. Ltd. (Mumbai, India) and SD Fine Chemicals Pvt. Ltd. (Mumbai, India) respectively. The reactions were monitored using precoated TLC silica gel F_{254} aluminum plates and solvents of different compositions were used as mobile phase. The spots were visualized using iodine chamber. Melting points were determined to its uncorrected value on capillary tubes by Thomas Hoover melting point apparatus. The compounds were characterized by IR, ^{1}H, ^{13}C Nuclear Magnetic Resonance Spectroscopy and Mass Spectrometry using Shimadzu FT-IR 157, Bruker NMR Spectrometer (300/400 MHz) and Agilent LC-MS Spectrometer respectively. Further, elemental analysis was done by Thermo Finnigan flash analyzer (EA 1112 CHNS).

The microbial strains-*Staphylococcus aureus* (ATCC11632), *Streptococcus faecalis* (ATCC 14506), *Bacillus subtilis* (ATCC 60511), *Klebsiella pneumoniae* (ATCC10031), *Escherichia* and *Pseudomonas aeruginosa* (ATCC10145), *Saccharomyces cerevisiae* (ATCC 9763, Sc), *Candida tropicalis* (ATCC 1369, CT) and *Aspergillus niger* (ATCC 6275) were obtained from American Type Culture Collection (ATCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India. HeLa (human cervix carcinoma cell line), A549 (Human lung adenocarcinoma cell line), MCF-7 (human breast adenocarcinoma cell line), A2780 (human ovarian cancer cell line), BGC-823 (human gastric cancer cell line) and L02 (human normal cell

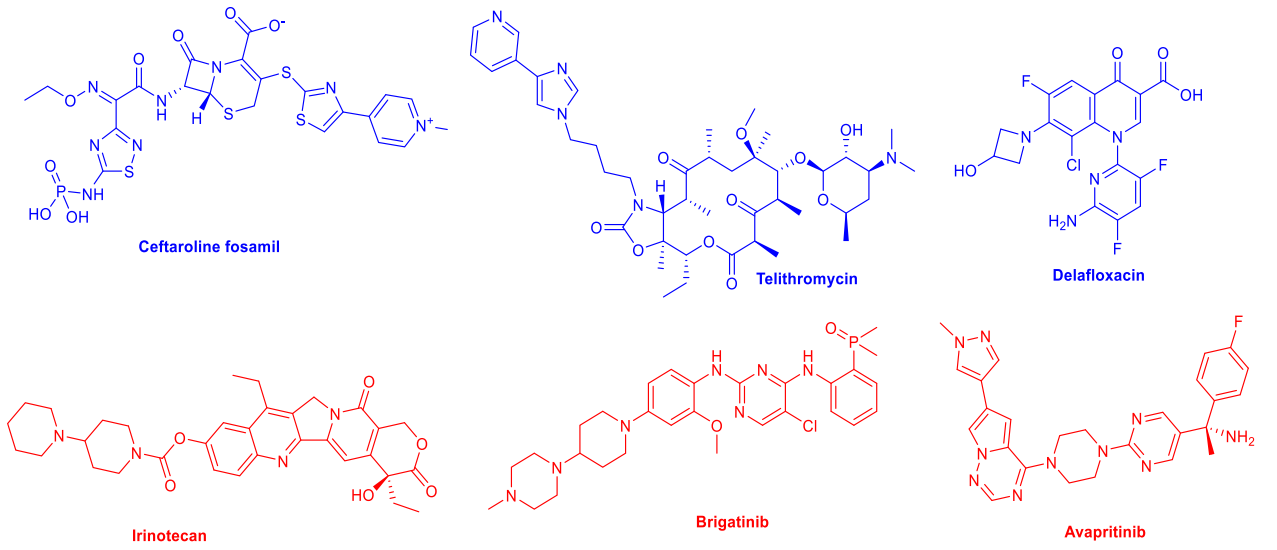


Fig. 1 Examples of drug molecules with antimicrobial (in Blue) and anticancer (in Red) drugs bearing multi-heterocyclic rings.

line) cell lines were procured from American Type Culture Collection (ATCC).

2.2. Experimental

*2.2.1. General procedure for the synthesis of 2-(2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydropyrazol-1-yl) thiazol-4-yl)acetohydrazide (**1**)*

The starting material **1** was prepared according to previously reported literature method [29]. Recrystallized from ethanol, Yellowish solid (Yield 75%); mp: 132–134 °C; IR (KBr) V_{max}/cm^{-1}: 1667 (C = O), 1568 (C = N), 1524 (C = C).^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.33 (s, 2H, thiazole-CH_2-triazole), 3.69–3.75 (dd, 1H, *J* 17.68, 6.28, pyrazole -CH_2), 3.90–3.98 (dd, 1H, *J* 17.72, 11.92, pyrazole-CH_2), 4.22 (s, 2H, -NH_2-, D_2O exchangeable), 5.74–5.78 (dd, 1H, *J* 11.84, 6.36, pyrazole-CH), 6.65 (s, 1H, -CH- thiazole), 6.66–6.67 (d, 1H, *J* 3.44, -CH- furan),7.15 (d, 1H, *J* 3.40, -CH- furan), 7.39 (t, 1H, *J* 7.96, -CH, dichlorobenzene), 7.50–7.82 (7H, dichlorobenzene, benzylidenimin), 9.04 (s, 1H, -NH-, D_2O exchangeable). LC-MS (*m*/*z*, %): 513.25 (M + 1, 17.4). Anal. calcd for $C_{24}H_{19}Cl_2N_5O_2S$: C, 56.34; H, 3.84; N, 13.78. Found: C, 56.26; H, 3.74; N, 13.67.

*2.2.2. General procedure for the synthesis of 5-((2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydropyrazol-1-yl) thiazol-4-yl)methyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (**2**)*

Compound **1** (0.20 mol), phenyl isothiocyanate (0.30 mol) were dissolved in ethanol (5 Volumes) and the mixture was stirred at 25 ± 30 °C and the mass was heated to reflux and stirred for 4 h, white solid formed was filtered. The resulting solid (0.20 mol) was dissolved in 2 N Sodium hydroxide solution and then the mass was heated to reflux and stirred for 3 h. The resulting solution was cooled to 25 ± 30 °C and acidified to pH 3–4 with using 36% hydrochloric acid. Recrystallized from ethanol, Yellowish solid (Yield 75%); mp: 190–192 °C; IR (KBr) V_{max}/cm^{-1}: 1630 (C = N), 1571 (C = C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.68–3.74 (dd, 1H, *J* 18.0, 6.0, pyrazole-CH_2), 3.81 (s, 2H, thiazole-CH_2-triazole), 3.85–3.90 (dd, 1H, *J* 16.0, 5.6, pyrazole-CH_2), 5.68–5.73 (dd, 1H, *J* 11.60, 6.40, pyrazole-CH), 6.27 (s, 1H, -CH-thiazole), 6.42–6.43 (d, 1H, *J* 3.60, -CH-furan), 7.13–7.14 (d, 1H, *J* 3.60, -CH- furan), 7.327.80 (13H, dichlorobenzene, benzylidenimin, triazole phenyl), 13.92 (1H-triazole-SH-). LC-MS (*m*/*z*, %): 630.24 (M + 1, 14.7). Anal. calcd for $C_{31}H_{22}Cl_2N_6OS_2$: C, 59.18; H, 3.56; N, 13.41. Found: C,59.14; H, 3.52; N, 13.35.

*2.2.3. General procedure for the synthesis of 5-((2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydropyrazol-1-yl) thiazol-4-yl)methyl)-1,3,4-oxadiazole-2-thiol (**3**)*

Potassium hydroxide (0.006 mol) and water (2 mL) mixture was stirred at 25 ± 30 °C. To the above solution, compound **1** (0.003 mol) was and stirred for 20 min at 25 ± 30 °C. Carbon disulfide (2 mL) was added to the reaction mixture and mass was heated to reflux and stirred mixture for 8 h. Solvent was removed completely and residue was treated with water and filtered. The filtrate was neutralized to pH 6 using dilute hydrochloric acid at 0 ± 5 °C, the separated product was filtered and washed with water. Recrystallized from ethanol, Pale yellowish solid (Yield 68%); mp: 154–156 °C; IR (KBr) V_{max}/cm^{-1}: 2763 (SH), 1615 (C = N), 1562 (C = C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.70–3.76 (dd, 1H, *J* 18.0, 6.8, pyrazole-CH_2), 3.87–3.95 (dd, 1H, *J* 18.0, 12.0, pyrazole-CH_2), 4.05 (s, 2H, thiazole, -CH_2-, oxadiazole), 5.70–5.75 (dd, 1H, *J*12.0, 6.40, pyrazole-CH), 6.57–6.58 (d, 1H, *J* 3.60, -CH- furan), 6.58 (s, 1H, -CH- thiazole), 7.09–7.10 (d, 1H, *J* 3.20, -CH-furan), 7.34–7.80 (8H, dichlorobenzene, benzylidenimin), 14.43 (s, 1H, SH-oxadiazole). LC-MS (*m*/*z*, %): 554.81 (M + 1, 9.6). Anal. calcd for $C_{25}H_{17}Cl_2N_5O_2S_2$: C, 53.30; H, 2.90; N, 13.26. Found: C, 52.28; H, 2.86; N, 13.25.

*2.2.4. General procedure for the synthesis 3-(subsituted)-5-((2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydropyrazol-1-yl)thiazol-4-yl)methyl)-4-phenyl-4H-1,2,4-triazole derivatives (**4a-e**)*

Compound **2** (0.010 mol), absolute ethanol and potassium hydroxide (0.025 mol) mixture was stirred at 25 ± 30 °C for 30 min. Commercially available substituted benzyl bromide

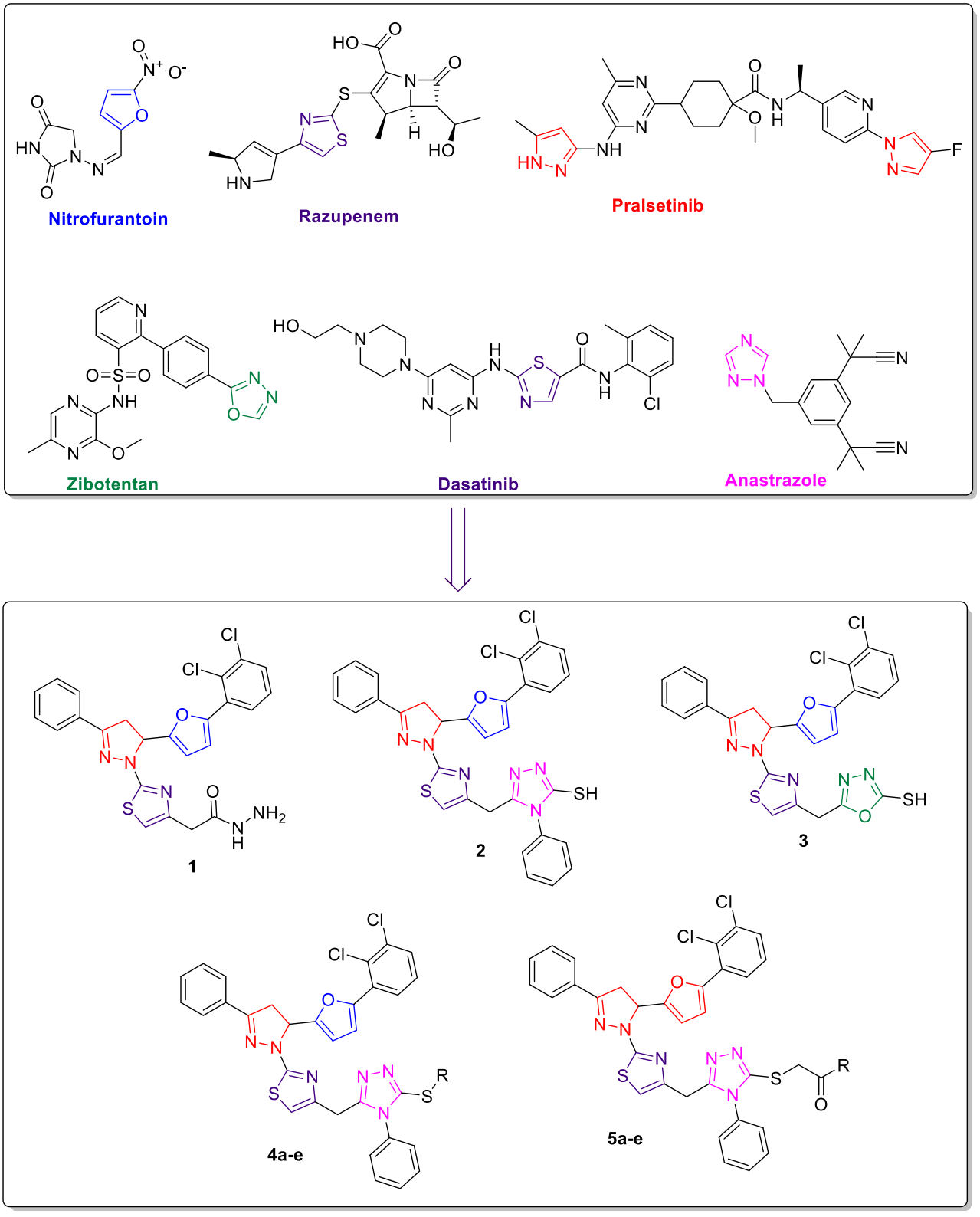


Fig. 2 Structures of selected antimicrobial and anticancer drugs containing furan, thiazole, pyrazole (oxidized form of pyrazoline), oxadiazole and triazole rings and the target compounds-**1**, **2**, **3**, **4a-e** and **5a-e**.

(0.011 mol) were added and the mixture was refluxed for 4 h. The completion of reaction was authenticated by TLC. The solvent in the mixture was evaporated under reduced pressure and the remained residue was quenched in to the water and filtered. The obtained solids were re-crystallized using suitable solvent to obtain target compounds (**4a-e**).

*2.2.4.1. 2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-4-((4-phenyl-5-(phenylthio)-4H-1,2,4-triazol-3-yl)methyl)thiazole (**4a**).* Recrystallized from ethanol, yellowish solid (Yield 81%); mp: 110–112 °C; IR (KBr) V_{max}/cm^{-1}: 1597 (C=N), 1581 (C=C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.65–3.71 (dd, 1H, J 17.72, 6.24, pyrazole-CH_2), 3.87 (s, 2H, thiazole-CH_2-triazole), 3.91–3.99 (dd, 1H, J 16.1, 7.8, pyrazole -CH_2), 4.50 (s, 2H, -S-CH_2-phenyl), 5.65–5.69 (dd, 1H, J 11.92, 6.36, pyrazole-CH), 6.29 (s, 1H, -CH- thiazole), 6.32–6.33 (d, 1H, J 3.44, -CH- furan), 6.94–6.95 (d, 1H, J 3.44, -CH- furan), 7.21–8.3 (18H, dichlorobenzene, benzylidenimin, triazole phenyl, benzyl); ^{13}C NMR (100 MHz, DMSO d_6) 22.6 (CH2, aliphatic), 38.5 (S-CH2), 38.1, 60.0 (pyrazole-CH2, CH), 101.0, 105.1 (furan-C2, C3), 104.3 (thiazole-C3), 127.0, 127.5 (dichlorobenzene-C6, C5), 127.2, 127.8 (S-CH2-phenyl-C4, C2,6), 128.1, 128.5 (phenyl-C2,6, C3,5), 128.8 (S-CH2-phenyl-C3,5), 128.7, 129.6 (phenyl- triazole-C3,4,5, C2,6), 130.8 (dichlorobenzene-C3), 131.0 (phenyl-C4), 131.5, 133.8 (dichlorobenzene-C2, C4), 136.4 (phenyl-C1),138.3 (dichlorobenzene-C1),139.7(S-CH2 phenyl-C1),145(phenyl-triazole-C1), 147.30 (triazole-C2), 150.1, 151.6 (furan-C1, C4), 151.7 (pyrazole-C), 153.0 (triazole-C1), 167.6 (C=N); LC-MS (*m*/*z*, %): 720.61 (M + 1, 13.5). Anal. calcd for $C_{38}H_{28}Cl_2N_6OS_2$: C, 63.46; H, 3.93; N, 11.70. Found: C, 63.42; H, 3.92; N, 11.68.

*2.2.4.2. 4-((5-((5-chloro-2-fluorophenyl)thio)-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)-2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazole (**4b**).* Recrystallized from ethanol, yellowish solid (Yield 79%); mp: 95–97 °C; IR (KBr) V_{max}/cm^{-1}: 1599 (C=N), 1583 (C=C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.66–3.72 (dd, 1H, *J* 17.70, 6.21, pyrazole-CH_2), 3.88 (s, 2H, thiazole-CH_2-triazole), 3.85–3.92 (dd, 1H, *J* 17.0, 7.2, pyrazole-CH_2), 4.50 (s, 2H, -S-CH_2-phenyl), 5.64–5.68 (dd, 1H, *J* 11.94, 6.38, pyrazole-CH), 6.28 (s, 1H, -CH- thiazole), 6.32–6.33 (d, 1H, *J* 3.44, -CH- furan), 6.93–6.94 (d, 1H, *J* 3.44, -CH- furan), 7.12–8.13; ^{13}C NMR (100 MHz, DMSO d_6) 22.6 (CH_2, aliphatic), 37.2 (S-CH_2), 38.2, 60.0 (pyrazole-CH_2, CH), 101.0, 105.2 (furan-C2, C3), 104.3 (thiazole-C3),116.9 (5-chloro-2-fuorobenzen-C3), 127.0, 127.5 (dichlorobenzene- C6, C5), 128.1, 128.5 (phenyl- C2,6, C3,5), 128.6, 128.9 (5-chloro-2-fuorobenzen-C1, C4), 128.7, 129.6 (phenyl-triazole-C3,4,5, C2,6), 129.9, 129.9 (5-chloro-2-fuorobenzen-C6,C5), 130.8 (dichlorobenzene-C3), 131.0 (phenyl-C4), 131.5, 133.8 (dichlorobenzene- C2,C4), 136.4 (phenyl-C1), 138.3 (dichlorobenzene-C1), 139.7(S-CH_2-phenyl-C1), 145 (phenyl-triazole-C1), 147.30 (triazole-C2), 150.1, 151.5 (furan-C1, C4), 151.7 (pyrazole-C), 153.2(triazole-C1), (5-chloro-2-fluoro benzen-C2),167.7 (C=N); LC-MS (*m*/*z*, %): 773.47 (M + 1, 16.2). Anal. calcd for $C_{38}H_{26}Cl_3FN_6OS_2$): C, 59.14; H, 3.42; N, 10.92. Found: C, 59.11; H, 3.39; N, 10.88.

*2.2.4.3. 2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-4-((4-phenyl-5-((2-(trifluoromethyl)phenyl)thio)-4H-1,2,4-triazol-3-yl)methyl)thiazole (**4c**).* Recrystallized from ethanol, yellowish solid (Yield 77%); mp: 85–87 °C; IR (KBr) V_{max}/cm^{-1}: 1594 (C=N), 1580 (C=C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.65–3.71 (dd, 1H, J 17.72, 6.24, pyrazole-CH2), 3.88 (s, 2H,thiazole-CH_2-triazole), 3.90–3.98 (dd, 1H, J 16.36, 9.24, pyrazole-CH_2), 4.50 (s, 2H, -S-CH_2-phenyl), 5.65–5.69 (dd, 1H, J 11.92, 6.36, pyrazole-CH), 6.28 (s, 1H, -CH-thiazole), 6.32–6.33 (d, 1H, J 3.44, -CH-furan), 6.93–6.94 (d, 1H, J 3.44, -CH- furan), 7.00–7.99 (17H, dichlorobenzene, benzylidenimin, triazole phenyl, benzyl); ^{13}C NMR (100 MHz, DMSO d_6) 22.7 (CH_2, aliphatic), 35.9 (S-CH_2), 38.2, 60.1 (pyrazole-CH_2, CH), 101.0, 105.3 (furan-C2, C3), 104.3 (thiazole-C3), 123.0 (CF_3), 126.2, 126.5, 127.4, 128.0 (2-trifluorobenzene-C3, C2, C4, C6), 127.0, 127.5 (dichlorobenzene-C6, C5), 128.1, 128.5 (phenyl- C2,6, C3,5), 128.7, 129.6 (phenyl- triazole-C3,4,5, C2,6), 129.9, 130.8 (dichlorobenzene- C3), 131.0 (phenyl-C4), 131.5, 133.9 (dichlorobenzene- C2, C4), 132.0 137.5 (2-triflorobenzene-C5, C1), 136.4 (phenyl-C1), 138.3 (dichlorobenzene-C1), 139.7 (S-CH_2-phenyl-C1), 145.5 (phenyl-triazole-C1), 147.30 (triazole-150.1,151.5 (furan-C1, C4), 151.6 (pyrazole–C), 153.0 (triazole-C1), 167.5 (C=N); LC-MS (*m*/*z*, %): 788.41 (M + 1, 10.6). Anal. calcd for $C_{39}H_{27}Cl_2F_3N_6OS_2$: C, 59.50; H, 3.52; N, 10.71. Found: C, 59.47; H, 3.45; N, 10.61.

*2.2.4.4. 2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-4-((4-phenyl-5-((4-(trifluoromethoxy)phenyl)thio)-4H-1,2,4-triazol-3-yl)methyl)thiazole (**4d**).* Recrystallized from ethanol, yellowish solid (Yield 78%); mp: 88–90 °C; IR (KBr) V_{max}/cm^{-1}: 1595 (C=N), 1583 (C=C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.66–3.72 (dd, 1H, J 17.75, 6.26, pyrazole-CH_2), 3.89 (s, 2H, thiazole-CH_2-triazole), 3.93–4.1 (dd, 1H, J 16.35, 8.5, pyrazole-CH_2), 4.30 (s, 2H, -S-CH_2-phenyl), 5.65–5.69 (dd, 1H, J 11.92, 6.36, pyrazole-CH), 6.28 (s, 1H, -CH-thiazole), 6.32–6.33 (d, 1H, J 3.44, -CH- furan), 6.93–6.94 (d, 1H, J 3.44, -CH-furan), 7.4–8.8 (17H,dichlorobenzene, benzylidenimin, triazole phenyl, benzyl); ^{13}C NMR (100 MHz, DMSO d_6)22.7 (CH2, aliphatic), 38.8 (S-CH2), 38.2, 60.1 (pyrazole –CH2, CH), 101.0, 105.3 (furan-C2, C3), 104.3 (thiazole-C3), 114.3 (4-trifluoro methoxybenzene-C3,5), 121.8 (O-CF3), 127.0, 127.5 (dichlorobenzene- C6, C5), 128.1, 128.5 (phenyl- C2,6, C3,5), 128.8 (4-trifluoromethoxybenzene-C2,6), 128.7, 129.6 (phenyl-triazole-C3,4,5, C2,6), 129.9, 130.8 (dichlorobenzene-C3), 131.0 (phenyl-C4), 131.5, 133.9 (dichlorobenzene-C2, C4), 132.0 (4-trifluoromethoxybenzene-C1), 136.4 (phenyl-C1), 138.3 (dichlorobenzene-C1), 139.7(S-CH2-phenyl-C1),145.5 (phenyl-triazole-C1), 147.30 (triazole-C1), 150.1,151.5 (furan-C1, C4), 151.6 (pyrazole-C), 153.0 (triazole-C1),159.1(4-trifluoromethoxybenzene-C4), 167.5 (C=N); LC-MS (*m*/*z*, %): 804.11 (M + 1, 11.3). Anal. calcd for $C_{39}H_{27}Cl_2F_3N_6O_2S_2$: C, 58.30; H, 3.41; N, 10.51. Found: C, 58.28; H, 3.39; N, 10.46.

*2.2.4.5. 2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-4-((5-((4-fluorophenyl)thio)-4-phenyl-4H-1,2,4-triazol-3-yl)methyl)thiazole (**4e**).* Recrystallized from ethanol, yellowish solid (Yield 80%); mp: 89–92 °C; IR (KBr) V_{max}/cm^{-1}: 1593 (C=N), 1580 (C=C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.65–3.71 (dd, 1H, J 17.78, 6.27, pyrazole-CH_2), 3.88 (s, 2H, thiazole-CH_2-triazole), 3.93–4.1 (dd, 1H, J 16.35,8.6, pyrazole-CH_2), 4.80 (s, 2H, -S-CH_2-phenyl), 5.65–5.69 (dd, 1H, J 11.92, 6.36, pyrazole-CH), 6.28 (s, 1H, -CH-thiazole), 6.32–6.33 (d, 1H, *J* 3.44 Hz, -CH- furan), 6.93–6.94 (d, 1H, J 3.44, -CH- furan), 7.05–8.0 (17H, dichlorobenzene, benzylidenimin, triazole phenyl, benzyl); ^{13}C NMR (100 MHz, DMSO d_6): 22.6 (CH_2, aliphatic), 38.5 (S-CH_2), 38.2, 60.1 (pyrazole-CH_2, CH), 101.0, 105.3 (furan-C2,

C3), 104.3 (thiazole-C3), 115.5 (4-fluorobenzene-C3,5), 127.0, 127.5 (dichlorobenzene-C6, C5), 128.1, 128.5 (phenyl-C2,6, C3,5), 129.4 (4-fluorobenzene-C2,6), 128.7, 129.6 (phenyl-triazole-C3,4,5, C2,6), 129.9, 130.8 (dichlorobenzene-C3), 131.0(phenyl-C4), 131.5, 133.9 (dichlorobenzene-C2, C4), 135.3 (4-fluorobenzene-C1), 136.4 (phenyl-C1), 138.3 (dichlorobenzene-C1), 139.7 (S-CH2-phenyl-C1),145.5 (phenyl-triazole-C1), 147.30 (triazole-C2), 150.1, 151.4 (furan-C1, C4), 151.6 (pyrazole-C),153.2 (triazole-C1), 161.3 (4-fluorobenzene-C4), 167.6 (C = N); LC-MS (*m*/*z*, %): 738.52 (M + 1, 15.1). Anal. calcd for $C_{38}H_{27}Cl_2FN_6OS_2$: C, 61.90; H, 3.70; N, 11.41. Found: C, 61.87; H, 3.69; N, 11.39.

*2.2.5. General procedure for the synthesis of 1-(substituted phenyl)-2-(5-((2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydropyrazol-1-yl)thiazol-4-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)ethanone derivatives (**5a-e**)*

Compound **2** (0.010 mol), absolute ethanol and potassium hydroxide (0.025 mol) mixture was stirred at 25 ± 30 °C for 30 min and commercially available substituted phenacyl bromide (0.011 mol) was added. The mixture was then refluxed for 4 h. Completion of reaction was confirmed by TLC. The solvent evaporated under reduced pressure, residue was quenched in to the water and filtered and the solid was further recrystallized with suitable solvent.

*2.2.5.1. 1-(4-bromophenyl)-2-((5-((2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)ethan-1-one (**5a**)*. Recrystallized from ethanol, off white solid (Yield 77%); mp: 162–164 °C; IR (KBr) V_{max}/cm^{-1}: 1679 (C = O), 1579 (C = C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.63–3.71 (dd, 1H, *J* 17.50, 6.44, pyrazole-CH_2), 3.83 (s, 2H, thiazole-CH_2-triazole), 3.87–3.95 (dd, 1H, *J* 16.64, 7.78, pyrazole-CH_2), 4.89 (s, 2H, -S-CH2-CO-phenyl), 5.64–5.70 (dd, 1H, *J* 11.73, 6.39, pyrazole-CH), 6.27 (s, 1H, -CH- thiazole), 6.35–6.36 (d, 1H, *J* 3.48 Hz,-CH-furan), 7.10–7.11 (d, 1H, *J* 3.39, -CH- furan), 7.14–8.20 (17H, dichlorobenzene, benzylidenimin, triazole phenyl, bromo phenyl); ^{13}C NMR (100 MHz, DMSO d_6): 22.6 (CH_2, aliphatic), 38.6 (S-CH_2), 38.2, 60.1 (pyrazole-CH_2, CH), 101.0, 105.3 (furan-C2, C3), 104.3 (thiazole-C3), 127.0, 127.5 (dichlorobenzene-C6, C5),127.7 (4-bromobenzene-C4), 128.1, 128.5 (phenyl-C2,6, C3,5), 128.7, 129.6 (phenyl- triazole-C3,4,5, C2,6), 129.9, 130.8 (dichlorobenzene-C3), 131.0, 131.6 (4-bromobenzene-C2,6, C3,5), 131.2 (phenyl-C4), 131.5, 133.9 (dichlorobenzene-C2, C4), 135.8 (4-bromobenzene-C1), 136.4 (phenyl-C1), 138.3 (dichlorobenzene-C1), 145.5 (phenyl-triazole-C1), 147.30 (triazole-C2), 150.1, 151.4 (furan-C1, C4), 151.6 (pyrazole-C), 153.0 (triazole-C1), 167.6 (C = N), 194.2 (C = O); LC-MS (*m*/*z*, %): 827.42 (M + 1, 9.8). Anal. calcd for $C_{39}H_{27}Cl_2N_6O_2S_2$: C, 56.71; H, 3.31; N, 10.20. Found: C, 56.67; H, 3.29; N, 10.17.

*2.2.5.2. 2-(5-((2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydropyrazol-1-yl)thiazol-4-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-ylthio)-1-(pyridin-2-yl)ethanone (**5b**)*. Recrystallized from ethanol, off white solid (Yield 86%); mp: 158–160 °C; IR (Kbr) V_{max}/cm^{-1}: 1685 (C = O), 1584 (C = C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.63–3.71 (dd, 1H, *J* 17.76, 6.42, pyrazole-CH_2), 3.83 (s, 2H, thiazole-CH_2-triazole), 3.86–3.95 (dd, 1H, *J* 16.08, 12.21, pyrazole-CH_2), 4.85 (s, 2H, -S-CH_2-CO-phenyl), 5.63–5.69 (dd, 1H, *J* 11.55, 6.18, pyrazole-CH), 6.26 (s, 1H, -CH- thiazole), 6.34–6.35 (d, 1H, *J* 3.39, -CH- furan), 7.10–7.11 (d, 1H, *J* 3.36, -CH-furan), 7.14–7.77 (14H, dichlorobenzene, benzylidenimin, triazole phenyl, Pyridine), 8.32–8.34 (d, 1H, *J* 8.19, - CH, Pyridine), 8.80–9.16 (s, 2H, - CH, Pyridine); ^{13}C NMR (100 MHz, DMSO d_6): 22.7 (CH_2, aliphatic), 38.2 (S-CH_2), 38.4, 60.0 (pyrazole-CH_2, CH), 101.0, 105.3 (furan-C2, C3), 104.1 (thiazole-C3), 123.7 (pyridine-C4), 127.0, 127.5 (dichlorobenzene-C6, C5), 128.1, 128.5 (phenyl-C2,6, C3,5), 128.7, 129.6 (phenyl-triazole-C3,4,5, C2,6), 129.9, 130.8 (dichlorobenzene-C3), 131.2(phenyl-C4),131.5,133.9 (dichlorobenzene-C2, C4), 132.2, 136.2 (pyridine-C2, C3), 136.4 (phenyl-C1), 138.3 (dichlorobenzene-C1), 145.5 (phenyl-triazole-C1), 147.30 (triazole-C2), 149.6, 149.9 (pyridine-C5, C1), 150.1,151.4 (furan-C1, C4), 151.5 (pyrazole-C), 153.0 (triazole-C1), 167.5 (C = N), 194.1 (C = O); LC-MS (*m*/*z*, %): 749.29 (M + 1, 12.5). Anal. calcd for $C_{38}H_{27}Cl_2N_7O_2S_2$: C, 61.00; H, 3.64; N, 13.13. Found: C, 60.96; H, 3.63; N, 13.10.

*2.2.5.3. 2-((5-((2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)-1-phenylethan-1-one (**5c**)*. Recrystallized from ethanol, off white solid (Yield 82%); mp: 160–163 °C; IR (Kbr) V_{max}/cm^{-1}: 1678 (C = O), 1573 (C = C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.63–3.71 (dd, 1H, J 17.49, 6.42, pyrazole-CH_2), 3.84 (s, 2H, thiazole-CH_2-triazole), 3.87–3.95 (dd, 1H, J 16.62, 7.77, pyrazole-CH_2), 4.85 (s, 2H, -S-CH_2-CO-phenyl), 5.64–5.70 (dd, 1H, J 11.73, 6.39, pyrazole-CH), 6.27 (s, 1H, -CH-thiazole), 6.35–6.36 (d, 1H, *J* 3.48 Hz,-CH-furan), 7.10–7.11 (d, 1H, J 3.39, -CH- furan), 7.15–8.10 (18H, dichlorobenzene, benzylidenimin, triazole phenyl, Phenyl); ^{13}C NMR (100 MHz, DMSO d_6): 22.7 (CH_2, aliphatic), 38.5 (S-CH_2), 38.2, 60.1 (pyrazole-CH_2, CH), 101.0, 105.3 (furan-C2, C3), 104.3 (thiazole-C3), 127.0, 127.5 (dichlorobenzene-C6, C5), 128.1, 128.5 (phenyl-C2,6, C3,5), 128.6, 128.8 (CO-phenyl-C2,6, C3,5), 128.7, 129.6 (phenyl- triazole-C3,4,5, C2,6), 129.9, 130.8 (dichlorobenzene- C3), 131.2 (phenyl-C4), 131.5, 133.9 (dichlorobenzene-C2, C4), 133.1, 135.4 (CO-phenyl-C4, C1), 136.4 (phenyl-C1), 138.3 (dichlorobenzene-C1), 145.5 (phenyl-triazole-C1), 147.30 (triazole-C2), 150.1, 151.4 (furan-C1, C4), 151.6 (pyrazole-C), 153.0 (triazole-C1), 167.6 (C = N), 194.1 (C = O); LC-MS (*m*/*z*, %): 748.56 (M + 1, 8.9). Anal. calcd for $C_{39}H_{27}Cl_2N_6O_2S_2$: C, 62.71; H, 3.78; N, 11.27. Found: C, 62.65; H, 3.77; N, 11.24.

*2.2.5.4. 1-(4-chlorophenyl)-2-((5-((2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)ethan-1-one (**5d**)*. Recrystallized from ethanol, off white solid (Yield 88%); mp: 166–168 °C; IR (Kbr) V_{max}/cm^{-1}: 1677 (C = O), 1574 (C = C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.64–3.72 (dd, 1H, *J* 17.48, 6.44, pyrazole-CH_2), 3.86 (s, 2H, thiazole-CH_2-triazole), 3.88–3.96 (dd, 1H, *J* 16.67, 7.8, pyrazole-CH_2), 4.86 (s, 2H, -S-CH_2-CO-phenyl), 5.64–5.70 (dd, 1H, *J* 11.74, 6.40, pyrazole-CH), 6.27 (s, 1H, -CH- thiazole), 6.35–6.36 (d, 1H, *J* 3.48, -CH- furan), 7.11–7.12 (d, 1H, *J* 3.40, -CH- furan), 7.17–8.12 (17H, dichlorobenzene, benzylidenimin, triazole phenyl, chloro Phenyl); ^{13}C NMR (100 MHz,

DMSO d_6): 22.6 (CH_2, aliphatic), 38.6 (S-CH_2), 38.2, 60.1 (pyrazole-CH_2, CH), 101.0, 105.3 (furan-C2, C3), 104.3 (thiazole-C3), 127.0, 127.5 (dichlorobenzene-C6, C5), 128.1, 128.5 (phenyl-C2,6, C3,5), 128.7, 129.6 (phenyl-triazole-C3,4,5, C2,6), 128.8, 130.2 (4-chlorobenzene-C2,6, C3,5), 129.9, 130.8 (dichlorobenzene-C2), 131.2 (phenyl-C4), 131.5, 133.9 (dichlorobenzene-C2, C4), 134.9 (4-chlorobenzene-C1), 136.4 (phenyl-C1), 138.3 (dichlorobenzene-C1), 138.7 (4-chlorobenzene-C4), 145.5 (phenyl-triazole-C1), 147.30 (triazole-C2), 150.1, 151.4 (furan-C1, C4), 151.8 (pyrazole-C), 153.1 (triazole-C1), 167.7 (C = N), 194.2 (C = O); LC-MS (*m*/*z*, %): 783.29 (M + 1, 14.1). Anal. calcd for $C_{39}H_{27}Cl_3N_6O_2S_2$: C, 59.90; H, 3.51; N, 10.78. Found: C, 59.89; H, 3.48; N, 10.74.

*2.2.5.5. 2-((5-((2-(5-(5-(2,3-dichlorophenyl)furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4-yl)methyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)-1-(4-fluorophenyl)ethan-1-one (**5e**).* Recrystallized from ethanol, off white solid (Yield 78%); mp: 170–172 °C; IR (KBr) V_{max}/cm^{-1}: 1678 (C = O), 1578 (C = C): ^{1}H NMR (400 MHz, DMSO d_6): δ *ppm* 3.65–3.73 (dd, 1H, J 17.50, 6.46, pyrazole-CH_2), 3.86 (s, 2H, thiazole-CH_2-triazole), 3.89–3.97 (dd, 1H, J 16.65, 7.75, pyrazole-CH_2), 4.86 (s, 2H, -S-CH_2-CO-phenyl), 5.64–5.70 (dd, 1H, J 11.75, 6.40, pyrazole-CH), 6.28 (s, 1H, -CH-thiazole), 6.36–6.37 (d, 1H, J 3.49, -CH- furan), 7.11–7.12 (d, 1H, J 3.40, -CH- furan), 7.20–8.18 (17H, dichlorobenzene, benzylidenimin, triazole phenyl, fluoro Phenyl); ^{13}C NMR (100 MHz, DMSO d_6): 22.7 (CH_2, aliphatic), 38.8 (S-CH_2), 38.2, 60.1 (pyrazole-CH_2, CH), 101.0, 105.3 (furan-C2, C3), 104.3 (thiazole-C3), 115.4 (4-fluorobenzene-C3,5), 127.0,127.5 (dichlorobenzene-C6, C5), 128.1, 128.5 (phenyl-C2,6, C3,5), 128.7, 129.6 (phenyl-triazole-C3,4,5, C2,6), 129.9, 130.8 (dichlorobenzene-C3), 130.4 (4-fluorobenzene-C2,6), 131.2 (phenyl-C4), 131.5, 133.9 (dichlorobenzene-C2, C4), 132.4 (4-fluorobenzene-C1), 136.4 (phenyl-C1), 138.3 (dichlorobenzene-C1), 145.5 (phenyl-triazole-C1), 147.30 (triazole-C2), 150.1,151.4 (furan-C1, C4), 151.6 (pyrazole-C), 153.0 (triazole-C1), 167.3 (4-fluorobenzene-C4), 167.6 (C = N), 194.2 (C = O); LC-MS (*m*/*z*, %): 766.52 (M + 1, 16.9). Anal. calcd for $C_{39}H_{27}Cl_2FN_6O_2S_2$:C, 61.21; H, 3.58; N, 11.01. Found: C, 61.17; H, 3.55; N, 10.98.

2.2.6. Biological evaluation

2.2.6.1. Antimicrobial activity. The *in vitro* antimicrobial assay for synthesized compounds **1, 2, 3, 4a-e**, and **5a-e** was performed through broth dilution method using bacterial standard strains of *Staphylococcus aureus* (ATCC11632), *Streptococcus faecalis* (ATCC 14506), *Bacillus subtilis* (ATCC 60511), *Klebsiella pneumoniae* (ATCC10031), *Escherichia* and *Pseudomonas aeruginosa* (ATCC10145) and antifungal activity against yeasts: *Saccharomyces cerevisiae* (ATCC 9763, Sc) and *Candida tropicalis* (ATCC 1369, CT) and fungal standard strains of *Aspergillus niger* (ATCC 6275) respectively. The standard strains of bacteria and fungal were cultured in Mueller-Hinton broth and Sabouraud medium tubes respectively. Series of test compound solutions ranging from 1 to 500 µg/mL were prepared in dimethyl sulfoxide (DMSO). Each set of both medium cultured tubes were arranged to inoculated with each test compound solutions having the concentration of 1, 2, 4, 8, 16, 31.25, 62.5, 125, 250 and 500 µg/mL, after inoculation of test solution under sterilized condition, incubate the tubes for 24 h at 37 °C. Positive control (Ciprofloxacin, Norfloxacin for Bacterial strains and Fluconazole for Fungal strains) and negative control (DMSO alone) also included in to assay. The minimum inhibitory concentration (MIC) values against each strain for each test compound was determined compared with positive controls [30].

2.2.6.2. Anticancer activity. The *in vitro* anticancer study for synthesized compounds **1, 2, 3, 4a-e**, and **5a-e** was performed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay [28] against HeLa (human cervix carcinoma cell line), A549 (Human lung adenocarcinoma cell line), MCF-7 (human breast adenocarcinoma cell line), A2780 (human ovarian cancer cell line), BGC-823 (human gastric cancer cell line) and L02 (human normal cell line) cell lines. The cell lines were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum, penicillin, streptomycin placed in 96-well plates at 100 µL provided with humidified at 5% CO2 to get the total volume with density of 1–2.5 × 10^4 cells per mL and were allowed to adhere for 24 h before treatment with tested drug solution (10^{-5}, 10^{-6}, 10^{-7} mol/L final concentration) in DMSO. Triplicate wells were treated with media and each concentration of test compounds. Cell viability was assayed after 96 h of continuous drug exposure with a tetrazolium (MTT) reagent. The supernatant medium on wells was removed, 150 µL of DMSO was added to each well. The plates were gently agitated using mechanical plate mixer to complete the color reaction, then the optical density of color produced in each well was measured at 570 nm using micro plate reader. The 50% inhibitory concentration (IC50) of test compounds was determined compared with Doxorubicin and Cisplatin standard controls.

2.2.7. Computational studies

2.2.7.1. Molecular docking. Schrödinger Suite release 2019-1 was used to perform the molecular modelling studies [31]. The protein crystal structures of DNA gyrase in complex with clorobiocin (PDB ID: 1KZN) [32], cytochrome P450 14 alpha-sterol demethylase in complex with fluconazole (PDB ID: 1EA1) [33], and epidermal growth factor receptor in complex with 4-anilinoquinazoline inhibitor (PDB ID: 1M17) [34], was retrieved from the RCSB Protein Data Bank. Further, the Protein Preparation Wizard (PPW) of the Maeströ was utilized to prepare all the proteins. Hydrogen atoms were added, appropriate protonation states were assigned to all the residues using Epik. The bound co-crystallized ligands were used to define the active sites of respective targeted proteins. All the ligands were built and optimized using Maestro Molecule Builder and OPLS_2005 force field in LigPrep modules of Schrödinger software, respectively. Further, the prepared ligands were docked at the active sites of targeted proteins using the standard protocol implemented in Maeströ.

2.2.7.2. In silico drug likeliness studies. To meet the requirements of the drug-likeliness, the properties of the most potent antimicrobial and anticancer compounds **4e** and **5e**, **3** and **4e** respectively, were evaluated for their in silico parameters including GI absorption, Lipinski rule of five as well as CYP2C19 CYP2D6 inhibition using SwissADME web [https://www.swissadme.ch/ (accessed on 11th Dec 2021)] (SwissADME, 2021).

3. Results and discussion

3.1. Chemistry

The steps involved in synthesis of titled compounds are illustrated in Scheme 1. All the compounds were synthesized with good yields, the intermediate **3** was achieved by adopting simple one pot procedure that involves the treatment of carbohydrazide**1** with carbon disulfide under strong basic conditions followed by acidification with dilute hydrochloric acid whereas the compound **2** bearing 1,2,4-triazole scaffold was synthesized through the reaction of **1** with phenyl isothiocyanate in alkaline medium using sodium hydroxide as catalyst. The compounds **4a-e** and **5a-e** were obtained by refluxing compound **2** with commercially available substituted benzyl bromide/phenacyl bromide by using sodium hydroxide and ethanol as a base and solvent respectively.

The ^{1}H NMR spectrum of **1, 2, 3, 4a-e**, and **5a-e** compounds, shows doublet of doublet at 5 3.50–3.72 ppm (J = 1 7.75–17.92 Hz), 5 3.80–4.04 ppm (J = 17.49–17.76 Hz), 5 5.65–6.07 ppm (J = 11.36–11.74 Hz) for H_A, H_B and H_X protons of -CH_2- and -CH- fragments of pyrazolines ring which is due to vicinal coupling of two non-equivalent protons at 4th position on pyrazolines ring. The NH_2 group was indicated by peak at 8.18 ppm chemical shift value in the ^{1}H NMR spectrum of compound **1**. Lack of resonance of NH and NH2 in ^{1}H NMR spectrum of compound **3** and strong absorption band at 2763 cm^{-1} due to SH of oxadiazole in IR spectra and (M + 1) peak at 554 in LC-MS spectra confirmed the formation of compound **3**. Similarly, the ^{1}H NMR spectra of the compound **2** showed the characteristic peaks at chemical shift value 13.92 due to SH proton. The absence of characteristic SH peak of compound **2** in IR and ^{1}H NMR spectra of 1,2,4-triazole derivatives (**4a-e** and **5a-e**), and appearance of characteristic -CH_2- protons absorptions at chemical shift 4.50 ppm confirmed the formation of target compounds. IR, LC-MS and elemental analysis data established the structures of target compounds.

3.2. Biological activity

3.2.1. Antimicrobial activity

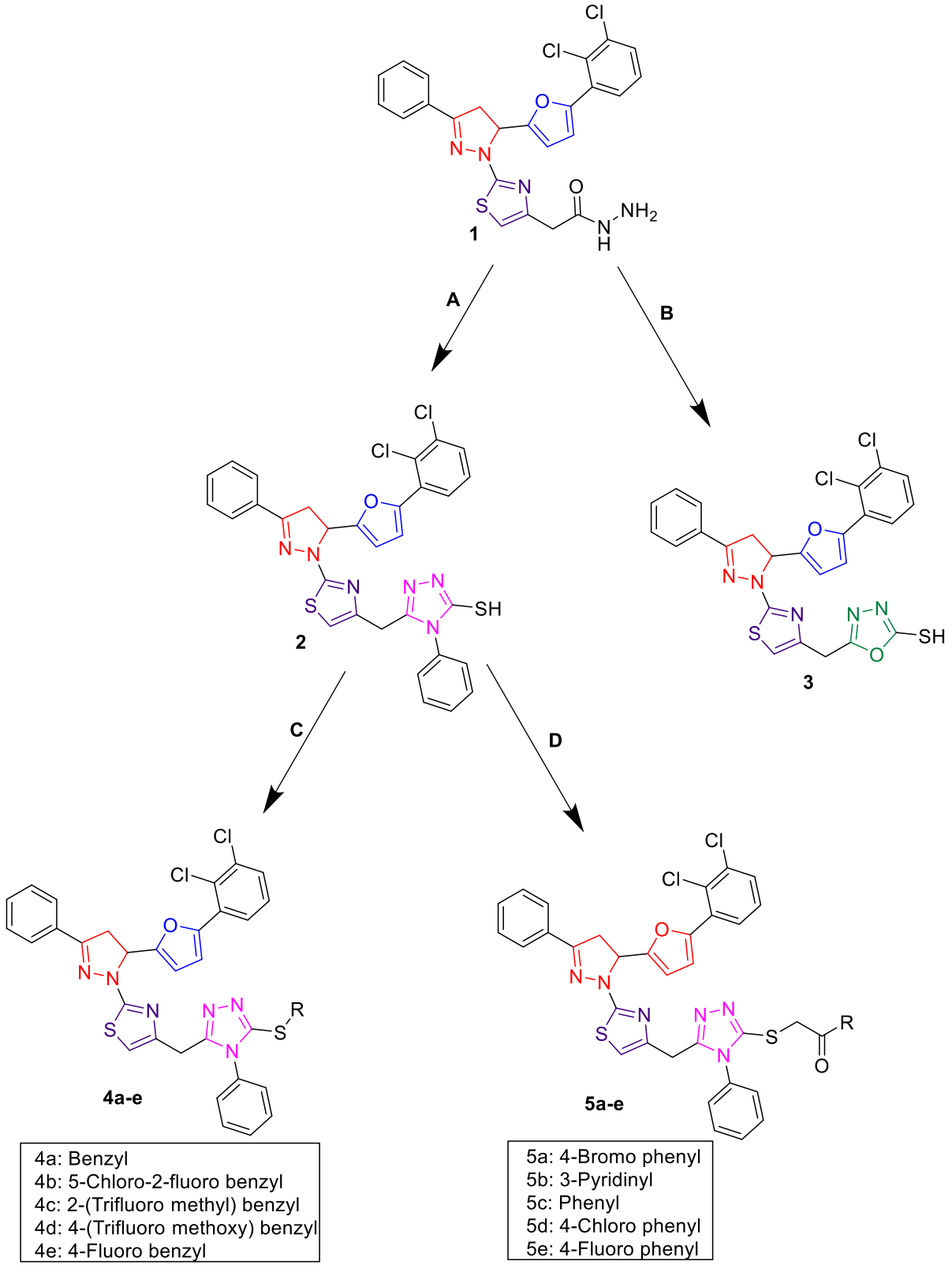
The results of the in vitro antimicrobial assay of titled compounds (**2, 3, 4a-e, and 5a-e**) against selected gram-positive, gram-negative bacteria, molds are illustrated in Table 1. All the compounds elicited considerable antimicrobial activity. This scenario suggests that the synthesized conjugated heterocyclic tetrads are useful antimicrobial candidates. However, there is a difference in the antimicrobial activity among the target compounds i.e., majority of the compounds displayed less activity than the standard drugs and few compounds showed promising antimicrobial activity. For instance, the compounds **4e** and **5e** belonging to 4th and 5th series that lack the free thiol functionality showed greater antimicrobial activity than the standard drugs against most of the tested microbial strains. The nature of the substituents on the phenyl ring connected to the sulfur is instrumental in altering the antimicrobial potency. The molecules **4e** and **5e** containing 4-fluoro substituent of smaller atomic radius showed excellent antibacterial and antifungal activities with MICs ranging from 0.5 to 8 μg/mL. However, other halogenated substituents containing a large volume are detrimental for the activity as the compounds **4c** (2-CF_3), **4d,** (4-OCF_3) **5d** (4-Cl) or **5a** (4-Br) antimicrobial potency was much less than the standard drugs with MICs ranging between 8 and 125 μg/mL. Additionally, their activity was less than the antimicrobial activity than plain phenyl ring compound **4a** & **5c**. Probably, the halogen reactivity at R position compromised the original interactions of non-substituted compounds with the bacterial target.

Structure activity relationship (SAR) studies of the synthesized compounds revealed that the phenyl ring and benzyl ring attached with the 1,2,4-triazole moiety is essential for antimicrobial activity. The compound **4a** consisting of benzyl ring at end terminal exhibit antimicrobial activity. Further studies revealed that the incorporation of halogens such as chloro and fluoro groups at position fifth and second in benzyl ring (**4b**) decreased the activity as compared to that of compound **4a**. Replacement of chloro group from 5th position and substitution of trifluoro groups at 2nd position in connection with alkyl group such as methyl in benzyl ring exhibit less activity than that of compounds **4a** & **4b**. The compound **4d** bearing trifluoro with electron releasing methoxy group at position 4th of the benzyl ring possesses moderate activity as compared to compound **4c**. The most potent antimicrobial compound of 4th series was **4e** which only consist of fluoro group at position 4th of the benzyl ring, this suggest that position 4th was favorable for substitution of fluoro group to enhance antimicrobial activity.

The 5th series comprised of substituted phenyl ring in end terminal with different halogens. The compound **5a** consist of bromo group at position 4th of the phenyl ring exhibit antimicrobial activity but less than that of compound **4a**. When pyridinyl group was incorporated at position-3 in the end terminal phenyl ring the activity was decreased. Further SAR studies revealed that when there was no substitution in the phenyl ring, the activity was again increased (**5c**). Replacement of larger halogen group (bromo; 5a) with chloro group at position 4th of the phenyl ring also reduces the activity. The antimicrobial activity was enhanced when smaller groups like fluorine alone was attached at position 4th of the phenyl ring. The SAR analysis also pointed the volume of halogen as a feasible restrictive factor since bromine, the largest halogen, is more deleterious to the antimicrobial activity than smaller fluorine (**4e** and **5e**). On comparison with both series of 4th & 5th, present studies revealed that compound **4e** and compound **5e** exhibit better antimicrobial activity among all other synthesized compounds. In addition, position fourth was the favorable point for the attachment of smaller halogens such as fluoro group to enhance antimicrobial activity. Based on the above data, we may infer that substituent (R) is a steric and/or restricted position that should be carefully considered in the future design of antimicrobial drug candidates.

3.2.2. Anticancer activity

All the titled compounds (**1**–**3**, **4a-4e** and **5a-5e**) were evaluated for their in vitro cytotoxic activity and anticancer activity against a panel of five cancer cell lines using doxorubicin and cisplatin as positive controls (Table 2). The in vitro cytotoxic activity and antiproliferative studies showed that the biological activity of these compounds depends on (i) the nature and site of substituents on aromatic ring (ii) effect of either substituted phenyl/phenyl-triazole all the compounds demon-



Scheme 1 Synthetic pathway for the preparation of target compounds-**2**, **3**, **4a-e** and **5a-e**.

Table 1 Antimicrobial activity expressed as MIC (μg/mL).

Compounds	Gram-positive organisms			Gram-negative organisms			Fungi		
	Sa	*Sf*	*Bs*	*Kp*	*Ec*	*Pa*	*Sc*	*Ct*	*An*
1	16	4	8	4	8	16	16	4	16
2	62.5	8	31.25	125	16	31.25	125	62.5	62.5
3	31.25	31.25	31.25	31.25	16	16	31.25	16	16
4a	**4**	8	**4**	**4**	8	8	62.5	125	62.5
4b	16	125	62.5	16	62.5	62.5	31.25	125	16
4c	62.5	62.5	62.5	125	125	125	125	8	8
4d	16	62.5	8	16	31.25	31.25	62.5	62.5	62.5
4e	**1**	**0.5**	**0.5**	**0.5**	4	8	**1**	2	**1**
5a	16	31.25	31.25	16	31.25	31.25	62.5	62.5	31.25
5b	31.25	31.25	62.5	62.5	62.5	62.5	62.5	62.5	125
5c	16	**4**	16	4	16	4	4	8	8
5d	31.25	31.25	31.25	31.25	125	16	31.25	16	125
5e	**4**	**0.5**	**8**	**8**	**1**	**2**	**4**	**1**	**2**
Ciprofloxacin	≤5	≤5	≤1	≤1	≤1	>5	–	–	–
Fluconazole	–	–	–	–	–	–	≤1	≤1	≤1

[a]The screening organisms. Gram-positive bacteria: *Staphylococcus aureus* (ATCC 11632, Sa), *Streptococus faecalis* (ATCC 14506, Sf), and *Bacillus subtilis* (ATCC 60511, Bs).
[b]The screening organisms. Gram-negative bacteria: *Klebsiella penumoniae* (ATCC 10031, Kp), *Escherichia coli* (ATCC 10536, Ec), and *Pseudomonas aeruginosa* (ATCC 10145, Pa).
[c]The screening organisms. Yeasts: *Saccharomyces cerevisiae* (ATCC 9763, Sc) and *Candida tropicalis* (ATCC 1369, Ct), mould: *Aspergillus niger* (ATCC 6275, An).

Table 2 Cytotoxicity of synthesized compounds against human tumour cells (IC_{50} ± SD, μM).

Compounds	Human tumour cells					Human normal cells
	Hela	A549	MCF-7	A2780	BGC-823	L02
1	**4.23 ± 0.23**	2.18 ± 0.45	**1.65 ± 0.44**	**2.12 ± 0.32**	1.34 ± 0.11	>40
2	**4.86 ± 0.49**	**1.21 ± 0.92**	2.50 ± 0.42	3.03 ± 1.54	1.20 ± 0.56	>40
3	**2.24 ± 0.48**	**1.39 ± 0.33**	3.76 ± 0.54	**1.56 ± 0.34**	**0.49 ± 1.45**	>40
4a	**5.02 ± 0.34**	3.98 ± 0.32	3.43 ± 0.33	2.88 ± 1.55	2.87 ± 0.55	>40
4b	**5.11 ± 0.55**	2.87 ± 0.44	3.12 ± 0.65	3.12 ± 0.55	2.08 ± 0.55	>40
4c	**3.98 ± 0.54**	2.09 ± 0.54	4.14 ± 0.58	5.76 ± 0.87	1.66 ± 0.54	>40
4d	**5.23 ± 0.67**	3.84 ± 0.48	2.74 ± 0.32	**1.57 ± 0.54**	2.54 ± 0.65	>40
4e	**1.43 ± 0.77**	**1.22 ± 0.45**	**0.65 ± 0.53**	**2.12 ± 0.44**	1.45 ± 0.28	>40
5a	7.23 ± 0.47	4.48 ± 0.84	2.34 ± 0.54	2.78 ± 0.56	1.22 ± 0.37	>40
5b	6.09 ± 0.33	**1.59 ± 0.42**	2.60 ± 0.48	3.93 ± 0.57	1.28 ± 0.30	>40
5c	6.45 ± 1.84	4.58 ± 0.11	2.94 ± 0.21	6.32 ± 1.25	3.35 ± 0.16	>40
5d	**5.13 ± 0.35**	**1.25 ± 0.87**	2.89 ± 0.35	5.51 ± 2.32	3.31 ± 0.54	>40
5e	**4.71 ± 0.24**	3.11 ± 0.64	**1.72 ± 1.98**	4.33 ± 1.59	1.97 ± 0.91	>40
Doxorubicin (control)	1.03 ± 0.22	0.67 ± 0.13	0.73 ± 0.25	0.95 ± 0.31	1.08 ± 0.15	>40
Cisplatin (Control)	5.65 ± 0.21	1.83 ± 0.62	1.85 ± 0.46	2.39 ± 0.47	0.98 ± 0.25	>40

strate anticancer effects with IC_{50} values comparable/better than the control Doxorubicin and Cisplatin. The key starting compound **1** containing three heterocyclic rings with carbohydrazide linkage had shown some level of anticancer activity against all the tested cell lines. However, the conversion of this molecule (**1**) into the corresponding heterocyclic tetrads-**2** and **3** had considerably improved the anticancer activity. Hence it could be concluded that the compounds **2** and **3** due to the presence of four heterocyclic scaffolds had improved binding interactions with the anticancer targets in the cancer cell and enhanced their activity. Among all the compounds, oxadiazole bearing heterocyclic tetrad **3** exhibited highest anticancer activity with an IC_{50} value of 0.49 ± 1.45 μM against the human gastric cancer cell line (BGC-823) and its activity was two-times greater than the standard drugs. The compounds lacking the acidic -SH group i.e., **4a-e** and **5a-e** series elicited reasonable activity compared to Doxorubicin and Cisplatin. Between these two series, compounds of **4a-e** series showed promising activity whereas **5a-e** ended with modest activity in comparison to Cisplatin. Within the **4a-e** series, the compound **4e** exhibited excellent anticancer activity against the breast cancer (MCF-7) cell line with an IC_{50} value of 0.65 ± 0.53 μM**.**

Structure activity relationship studies revealed that the four heterocyclic rings were essential for anticancer activity for both the series (**4a-e**, **5a-e**). However, the less activity of compounds in 5a-e series when compared to **4a-e** series represents that additional carbonyl group of the **5a-e** series compounds had diminished the important interactions due to steric and elec-

tronic reasons. The ring pyrazole played an important role for the anticancer activity. 1,2,4-Triazole nucleus in connection with benzyl & phenyl ring was vital for anticancer activity. However, their substitution pattern gave different results in which compound **4e** with benzyl ring and fluoro group at position 4th gave maximum anticancer activity. Likewise, in antimicrobial activity, here also flouro group at position 4th of the benzyl and phenyl ring of 4th and 5th series was essential for anticancer activity. All compounds were found to be non-toxic against human normal liver cell line (LO2) and the summary of the most active antimicrobial and anticancer compounds shown in Fig. 3 whereas the SAR features of the potent antimicrobial and anticancer compound 4e are summarized in Fig. 4.

3.3. Computational studies

3.3.1. Molecular docking

Similar scaffolds have been reported earlier for their potent anti-microbial, anti-fungal, and anti-cancer activities. This encouraged us to execute a computational molecular docking study to understand the interaction between the active compounds with the key targets by using GLIDE docking module of Schrödinger suite. Nisheeth et al. synthesized pyrazole, pyrazoline clubbed pyridine as potential antimicrobial agents and also performed a molecular docking study for the most active analogues against DNA gyrase enzyme [35]. Saeed et al. reported 3-(1,2,4-triazol-1-yl)flavanones as antifungal

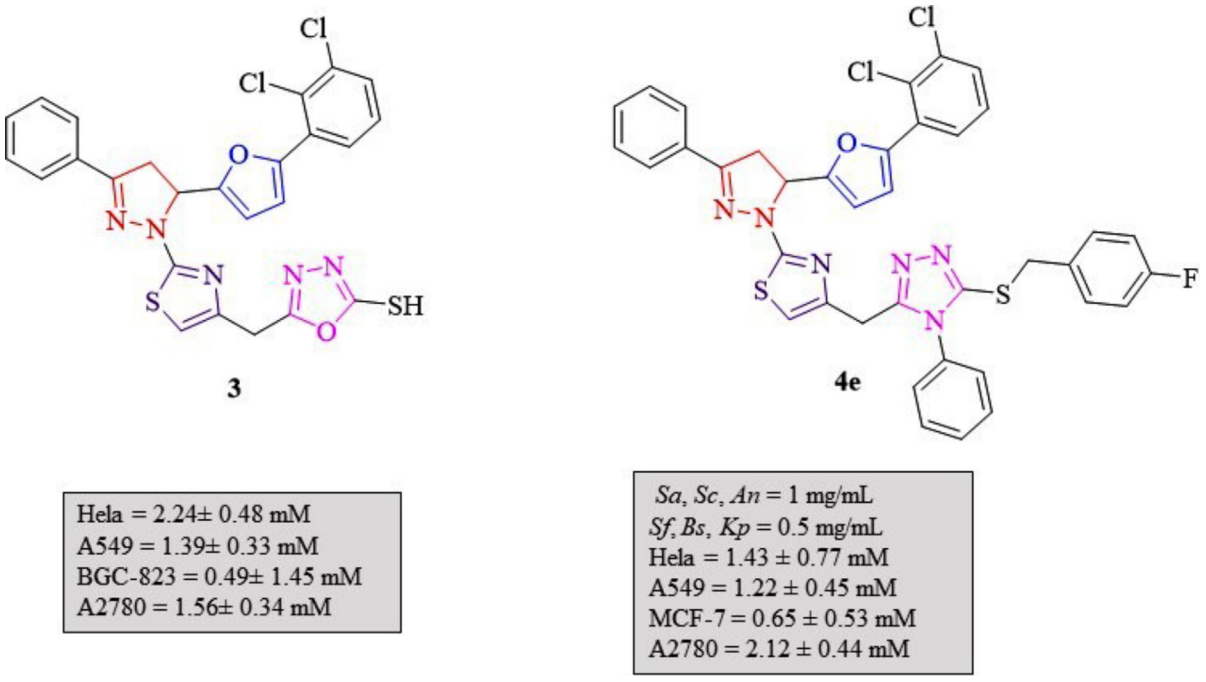


Fig. 3 Structure of most potent antimicrobial and anticancer compound.

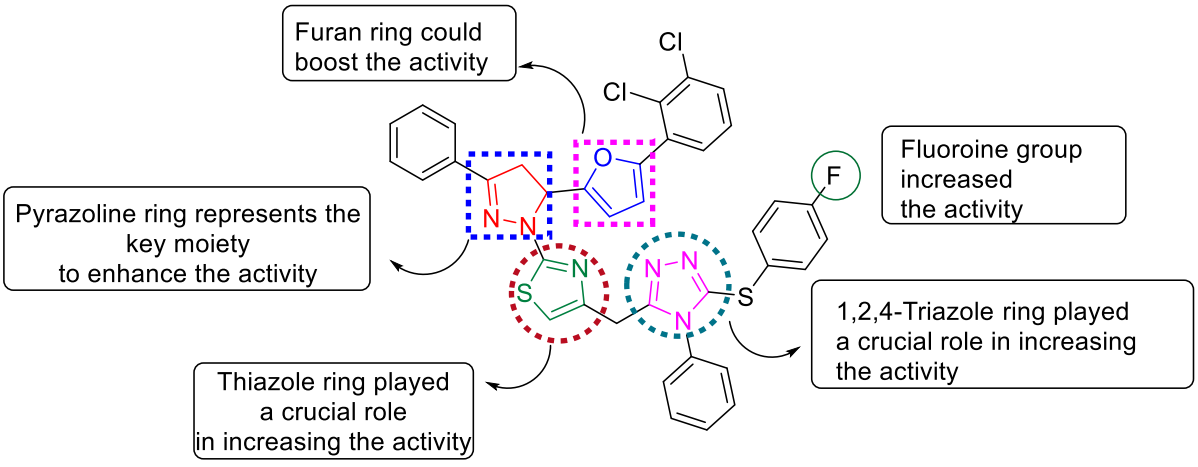


Fig. 4 SAR of most potent antimicrobial/anticancer compound **4e**.

agents and also elucidated the binding interactions of lead compounds with cytochrome P450 14 alpha-sterol demethylase by in silico studies [36]. Peng et al. synthesized thiazolyl-pyrazoline derivatives as EGFR TK inhibitors and potential anticancer agents [37]. Based on the literature, we have performed molecular docking studies by selecting DNA gyrase, cytochrome P450 14 alpha-sterol demethylase, and EGFR TK as targets for the anti-microbial, anti-fungal and anti-cancer activities, respectively.

The docking results along with the major interactions for the synthesized lead compounds **4e, 3** with the respective targeted proteins were depicted in Table 3. As shown in Fig. 5, compound **4e** well interacted with the active site of DNA gyrase. One of the chlorine atoms of dichlorophenyl moiety of compound **4e** has established a halogen bond interaction with the active site residue Arg136 with a distance of 2.64 Å. Captivatingly, the nitrogen atom of thiazole core of compound **4e** has formed a water-mediated hydrogen bonding interaction with active site amino acid residue Asp49. Additionally, several hydrophobic interactions were observed between the compound and the active site residues, e.g., Val43, Ala47, Val71, Ile78, Pro79, Ile90, Met91, Ala96, Val118, Val120 and Val167 are the other residues that stabilized the binding of the compound **4e** in the active site of DNA gyrase.

Table 3 GLIDE docking results for the synthesized compounds at the active site of selected disease targets.

Pharmacological activity	Targeted enzyme	Ligand name	Docking score	Interactions			
				H-bonds	Halogen bond	Hydrophobic	π – cation
Anti-microbial	DNA gyrase	**4e**	−5.697	–	Arg136	Val43, Ala47, Val71, Ile78, Pro79, Ile90, Met91, Ala96, Val118, Val120, Val167	–
Anti-fungal	14-alpha - sterol demethylase	**4e**	−6.865	–	–	Tyr76, Phe78, Met79, Phe83, Leu100, Leu105, Phe255, Ala256, Pro320, Leu321, Leu324, Pro349, Ile385, Pro386, Phe387, Cys394, Val395	Arg95, Arg96
Anti-cancer	Epidermal Growth Factor Receptor	**3**	−4.686	Met769	Cys773	Leu694, Ph699, Val702, Ala719, Leu768, Met769, Pro770, Phe771, Cys773, Tyr777, Leu820	–

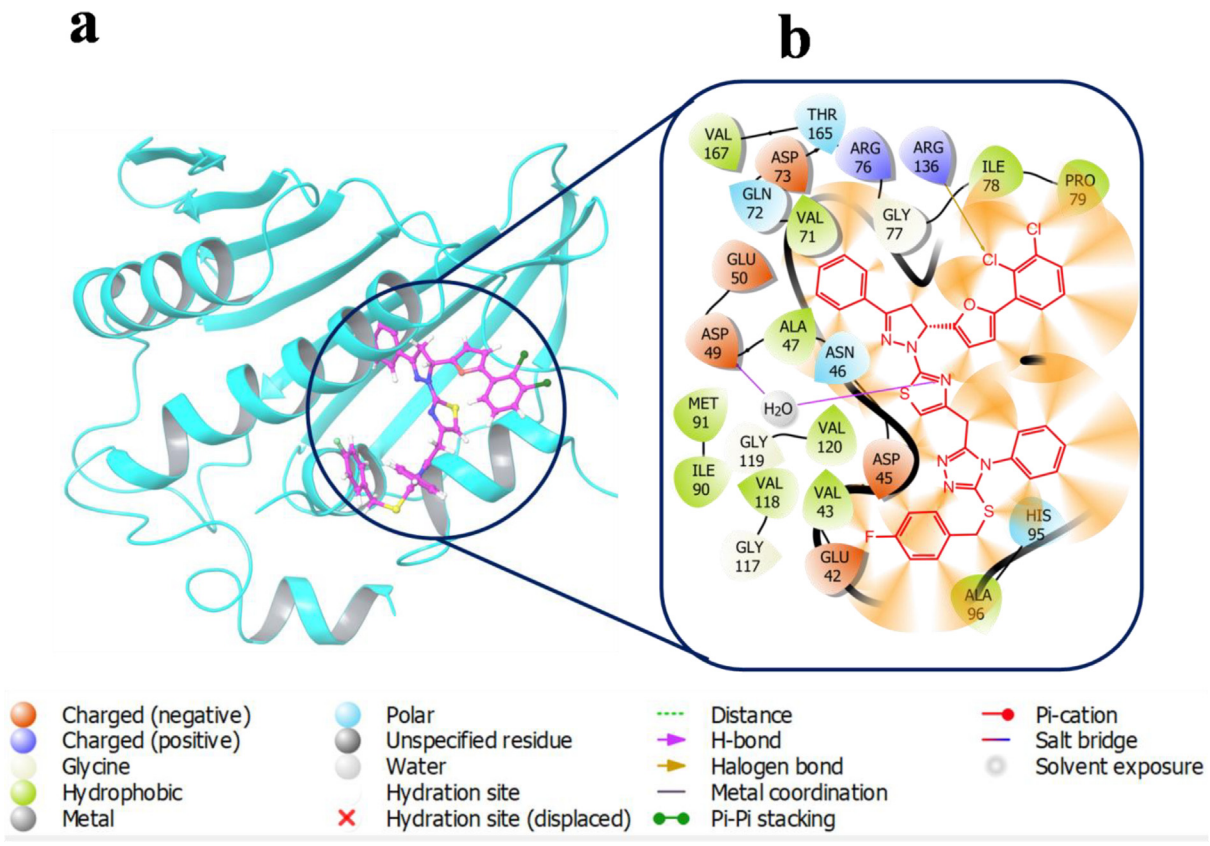


Fig. 5 (a) Docking pose of compound 4e (purple colour stick) and (b) its ligand–protein interactions in the active site of DNA gyrase (PDB ID: 1KZN).

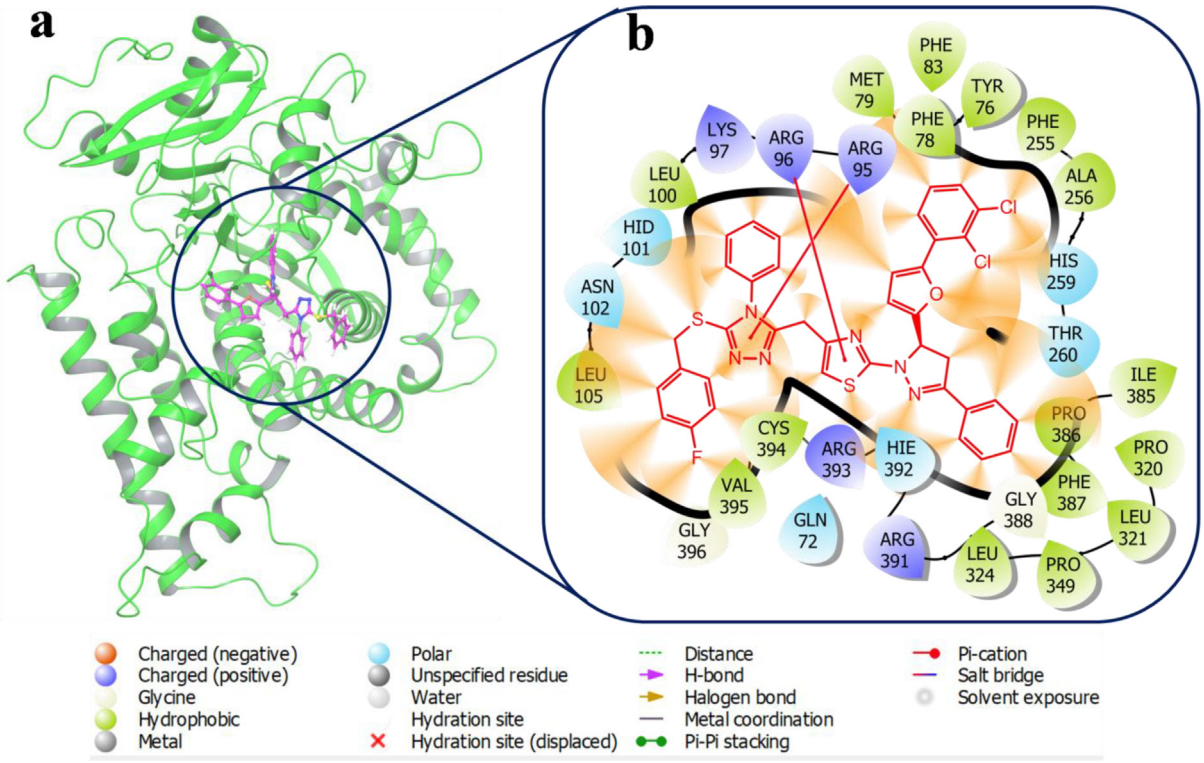


Fig. 6 (a) Docking pose of compound 4e (purple colour stick) and (b) its ligand–protein interactions in the active site of Cytochrome P450 14 alpha-sterol demethylase (PDB ID: 1EA1).

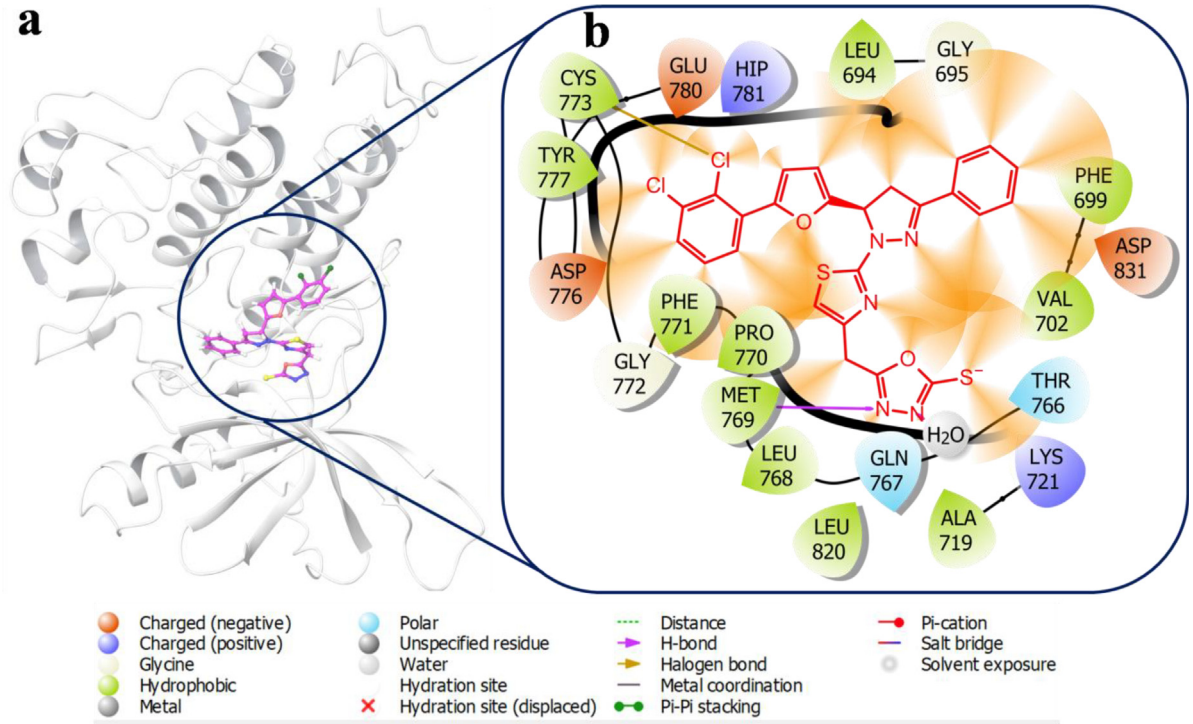


Fig. 7 (a) Docking pose of compound 3 (purple colour stick) and (b) its ligand–protein interactions in the active site of epidermal growth factor receptor (PDB ID: 1M17).

Table 4 Computed properties of compounds 3 and 4e using SWISSADME.

Compound #	GI Absorption	CYP2C19 inhibitor	CYP2D6 inhibitor	Lipinski #violations
4e	low	No	No	2
3	low	Yes	No	1

Furthermore, compound **4e** was also docked against the active site ofCYP450-14-alpha-sterol demethylase and Fig. 6 illustrates the predicted binding mode and the detailed protein–ligand interactions of compound **4e** with the active site of CYP450-14-alpha-sterol demethylase. Compound **4e** well interacted with the active site of CYP450-14-alpha-sterol demethylase by two π-cation (arene-cation) interactions. 1,2,4-triazole and thiazole moieties of compound **4e** have made π-cation interaction with the active site residues Arg95 (d = 4. 29 Å) and Arg96 (d = 5.75 Å), respectively. A number of hydrophobic interactions were observed between the compound **4e** and the active site residues, i.e., Tyr76, Phe78, Met79, Phe83, Leu100, Leu105, Phe255, Ala256, Pro320, Leu321, Leu324, Pro349, Ile385, Pro386, Phe387, Cys394 and Val395.

For a better understanding of the anti-cancer activity of compound **3**, we have performed a docking study on the active site of the epidermal growth factor receptor. Compound **3** was well accommodated at the active site of EGFR and its binding pose and interactions were shown in Fig. 7**.** One of the chlorine atoms of dichlorophenyl moiety of compound **3** has established a halogen bond interaction with the active site residue Cys773 with a distance of 3.46 Å. The nitrogen atom of the 1,3,4-oxadiazole moiety of compound **3** acts as a hydrogen bond acceptor and made an H-bond contact with the active site residue Met769 with a distance of 2.62 Å. Further, compound **3** has shownappreciable hydrophobic interactions with Leu694, Ph699, Val702, Ala719, Leu768, Met769, Pro770, Phe771, Cys773, Tyr777 and Leu820. From the molecular docking study, it was found that the compounds **4e** and **3** were well accommodated in the active pockets of targeted proteins and also made favourable interactions with their key residues. These findings were beneficial for the structure optimization of lead compounds.

3.3.2. In silico drug likeliness studies

Some selected compounds which showed the best activity in antimicrobial studies (**4e**), which showed the best anticancer (**3** and **4e**) activity were computed for certain properties using web based SwissADME software (Table 4). It can be observed that none of the compounds except **3** inhibited CYP2C19. None of the compounds inhibited CYP2D6. All compounds showed low GI absorption and did not pass Lipinski Rule of five and hence warrants further optimization for our future studies to improve the physicochemical properties.

4. Conclusions

Multi-step organic synthesis had led to the synthesis of target heterocyclic tetrad compounds-**1**, **2, 3, 4a-e** and **5a-e**. The synthesized compounds were screened against selected microbial strains and cancer cell lines for their antimicrobial and anticancer activities. Compound **4e** and **5e** possessing 4-fluoro phenyl and 4-fluoro benzyl moieties respectively displayed potent antimicrobial activities. Additionally, compound **4e** exhibited potential anticancer activity against breast cancer (MCF-7) cell line with IC_{50} value of 0.65 ± 0.53 μM. On the other hand, oxadiazole bearing compound **3** was potent against human gastric cancer cell line (BGC-823, IC_{50} = 0.49 ± 1.45 μM). Docking studies demonstrated that **4e** and **3** had substantial binding interactions with microbial and cancer proteins. All compounds showed no toxicity against human normal liver cell lines. Compounds **3** and **4e** have the potential to be attractive lead compounds for future research.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgment

The authors received no external funding for the research. However, RRB is thankful for Deanship of Graduate Studies and Research, Ajman University for providing partial funding towards the APC.

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